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EXAMINER	
SCHNIZER, HOLLY G	

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/559,344	Applicant(s) NEGRIER ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of th Claims

The Amendment After-final filed April 28, 2003 has been entered and considered. Claim 14 has been cancelled. Therefore, Claims 1-13 are pending and have been considered in this Office Action.

Reconsideration of the claims has revealed an oversight that requires an additional rejection that would bring up a new issue. Therefore, the finality of the rejection is withdrawn.

Drawings

The drawings have been approved by the draftsperson.

Rejections Withdrawn

The rejection of Claim 2 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn in light of the amendment to the claim.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al. (Human Gene Therapy (July 1995) 6: 873-880) in view of Uzan et al. (J. Biol. Chem. (1991) 266(14): 8932-8939) and Romp et al. (Blood Coagulation and Fibrinolysis (1993) 4: 905-910).

A response to Applicants arguments follows a statement of the rejection.

Rejection

Hao et al. teaches a DNA construct for the expression of *factor IX* in a *hematopoietic* cell line (HL-60 cells; p. 877, Col. 2) comprising DNA coding for a blood coagulation factor (FIX) and a process of using the construct to express factor IX in a hematopoietic cell line (HL-60; see abstract). Hao et al. suggests *using hematopoietic-specific promoters* (p. 879, Col. 1, lines 27-28). Hao et al. also *teaches induction of expression with PMA* in HL-60 cells (p. 878, Table I).

Hao et al. does not teach specifically using the GPIIb promoter but does suggest using hematopoietic specific promoters to express factor IX in general.

Uzan et al. provides a characterization of the *GPIIb promoter* and concludes that the GPIIb promoter contains sufficient information to direct tissue specific expression and suggests that this promoter can be used to target expression of heterologous genes in *megakaryocytes* (hematopoietic cells; see p. 8932, 1st paragraph of intro. And p. 8938, Col. 2, last two lines). Uzan et al. teaches the tissue specific expression of the CAT gene using the GPIIb promoter in the human erythroleukemia (HEL) cell line (considered a megakaryocyte cell line and the cell line described in the present Specification as being used to test megakaryocytic promoter expression; see p. 5, 1st paragraph of Specification).

Romp et al. teaches that platelets contain factor IX that is released by thrombin activation and suggest that platelets may be able to transport factor IX to sites of injury while protecting it from inactivation by antibodies (see p. 910, Col. 1, last paragraph). Romp et al. also teach that only a small amount of factor IX might significantly improve the effectiveness of haemostasis when plasma factor IX is deficient (p. 910, Col. 1, last paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the DNA construct taught in Uzan et al. for the expression of factor IX as taught in Hao et al. and use the DNA construct in a method of making factor IX in the megakaryocyte HEL cell as taught in Uzan et al.. One would have been motivated to make such a DNA construct and use it to produce Factor IX

because Hao et al. teaches that there is a need to improve the current systems of gene delivery of factor IX and suggests using hematospecific promoters to achieve persistent in vivo expression in hematopoietic cells. DNA constructs comprising a hematopoietic-specific promoter and a sequence coding for Factor IX are desirable for use in transfecting hematopoietic cells to be used in the treatment of hemophilia because they are more readily obtained than other cells, such as hepatocytes (see p. 878, Discussion, paragraph bridging Col. 1 and 2). Moreover, megakaryocytes (the precursors of platelets) would be a desirable choice for tissue specific expression of factor IX because it would allow the placement of factor IX in platelets (which are derived from the megakaryocytes) where it would be protected from inactivation by antibodies, as discussed in Romp et al. and where it could act specifically at the site of bleeding and at the time of bleeding (by regulated factor IX release following platelet activation at sites of injury). Thus, it appears that the claims are unpatentable over the prior art. The first step in designing an effective gene delivery system is to develop a model in vitro. Uzan et al. show that the GPIIb promoter is capable of controlling tissue-specific expression of the heterologous gene, CAT, in HEL cells. Therefore, the first step would be to develop an in vitro model of tissue specific expression of factor IX by replacing the CAT gene in the Uzan et al. construct with DNA encoding factor IX. One of ordinary skill at the time of the invention would have had a reasonable expectation of success in doing so because of the success described in Uzan et al. with the CAT gene and because of the success of tissue specific expression of factor IX in other types of cells (see Hao et al., p. 879, Col. 1, lines 29-30).

Applicants argue that there is no motivation to combine Uzan et al. and Hao et al. because Hao et al. does not require targeted expression in vivo. This argument has been considered but is not deemed persuasive for the following reasons.

Applicant still appears to be arguing against the references individually rather than considering what they teach as a whole and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The ultimate goal of the Hao et al. research is to engineer a cell to produce and secrete sufficient levels of a functional clotting factor that could act as a continuous in vivo source. As part of this research, Hao et al. show that successful expression of factor IX in a hematopoietic cell line can be achieved using the Moloney murine leukemia virus long terminal repeat (vector LIXSN) or the cytomegalovirus promoter (vector LIXCIX) (see paragraph spanning p. 877-888 and Table I). Hao et al. suggests improving on this success using hematopoietic specific promoters (see p. 878, Col. 2, last paragraph and p. 879, Col. 1, first paragraph, and p. 879, Col. 1, lines 27-28). Hao et al. states that "the use of hematopoietic-specific promoters may result in persistent in vivo expression in the hematopoietic cells, as have muscle-specific promoters in myoblasts" (p. 879, Col. 1, lines 27-30). Applicants argument that Hao et al. teaches removal of specific cells of interest from the body, transducing ex vivo, and then reimplanting them would not require targeted expression and that Hao et al. teaches away because such targeting may result in insufficient production of factor IX is not found persuasive. Hao et al.

teaches that while it would be ideal to be able to transduce the factor IX gene into all the stem cells in a marrow inoculum, in practice, researchers have only been able to achieve transduction in 1-2% of the stem cells (p. 878, Col. 2, last paragraph). Hao et al. suggests that only a fraction of transduced mature blood cells would be sufficient to correct a coagulation defect, if the synthetic capacity of the cells is adequate (see p. 879, 1st paragraph). Romp et al. teach that only a few percent of normal plasma factor IX levels are required to support haemostasis in the absence of significant trauma and that localized release of a small amount of factor IX might significantly improve the effectiveness of haemostasis when plasma factor IX is deficient (p. 910, Col. 1, last paragraph). One of ordinary skill in the art with the combined teachings of Hao et al., Uzan et al. and Romp et al. would recognize that expression of factor IX in megakaryocytes (the precursor to platelets) would be one way to achieve the localized release of factor IX at the site of injury and would be a way to overcome all of the obstacles of low transduction described in Hao et al.

Applicants argument that there is no reasonable expectation of success because Uzan et al. does not know whether the GPIIb promoter could be used to target expression of heterolgous genes other than itself is not found to be persuasive because Uzan et al. describe the tissue specific expression of the heterologous gene, CAT using the GPIIb promoter (see entire reference). On the contrary, one of ordinary skill in the art at the time of the invention having the Hao et al., Uzan et al., and Romp et al. references in hand would have had a reasonable expectation of success because of the success described in Uzan et al. with the CAT gene and because of the success of tissue

specific expression of factor IX in other types of cells (see Hao et al., p. 879, Col. 1, lines 29-30). Moreover, with Hao et al. suggestion to use hematopoietic specific promoters in the production of factor IX, one of skill in the art would have been motivated to use the GPIIb promoter taught in Uzan et al. because it was shown to be specific for megakaryocytes .

Thus, for the reasons stated above and in the previous Office Actions, the claims appear to be unpatentable over Hao et al. and Uzan et al. in view of Romp et al.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al. Uzan et al., and Romp as applied to claims 1-3 and 5-14 above, and further in view of Kurachi et al. (J. Biol. Chem. (1995) 270(10): 5276-5281; cited in IDS of Paper No. 2).

The teachings of Hao et al., Uzan et al., and Romp et al. have been described above.

Hao et al., Uzan et al., and Romp et al. do not teach a DNA construct wherein Intron 1 of the human factor IX gene is inserted into the factor IX cDNA.

Kurachi et al. teach a construct encoding human factor IX wherein the first intron of human factor IX is inserted into the factor IX cDNA and wherein the Intron I sequence enhances transgene expression by protecting spliceosome complexes from random degradation (see abstract and figure 2, p. 5278).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add an Intron I sequence of factor IX to a DNA construct comprising a tissue specific promoter and a sequence coding for factor IX as taught

and suggested in Hao et al. and Uzan et al. One would be motivated to insert the Intron I sequence into the factor IX cDNA because, as Kurachi et al. teach, the first intron of Factor IX functions to enhance gene expression. Thus, it appears that the claims are unpatentable over the prior art.

Applicants have addressed this rejection (see p. 6 of Paper No. 15) along with the rejection of the claims 1-3 and 5-14under 35 U.S.C. 103(a) as obvious over Hao et al. in view of Uzan et al. and Romp et al. given above. Thus, the response to applicants' arguments concerning this rejection is the same as that given above for claims 1-3 and 5-14.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for the production of Factor IX in a hematopoietic cell line in vitro, does not reasonably provide enablement for a process for the production of Factor IX in hematopoietic cells in vivo (gene therapy). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims and Nature of the Invention:

Claim 5 is drawn to a process for the production of Factor IX in hematopoietic cells and encompasses in vivo expression and gene therapy. The Specification implies that one of the specific utilities of such a process is in a treatment of Hemophilia B by gene therapy (see Specification at p. 1, 3rd paragraph and p. 2, 4th paragraph).

The Amount of direction or guidance presented only involves in vitro expression of factor IX in megakaryocyte cell lines such as HEL cells.

The specification does not teach or provide guidance as to how to successfully produce factor IX *in vivo* in hematopoietic cells to be successfully used therapeutically. There is no guidance concerning the type of delivery vehicle/vector system that would successfully deliver DNA encoding factor IX to the appropriate tissue and result in successful expression of factor IX in vivo.

There are no working examples of a method of producing factor IX in vivo.

The Specification only provides working examples of methods of producing Factor IX in a Human Erythroleukemia (HEL) cell line (indicated on page 5, 1st paragraph as being classical cell line used to test megakaryocytic promoter expression) *in vitro* using DNA constructs comprising DNA encoding factor IX operably linked to the human platelet glycoprotein IIb (GPIIb) promoter.

State of the Prior Art and Relative Skill of those in the Art

As evidenced in the obviousness rejection above, those of skill in the art would recognize that a DNA construct comprising the sequence coding for Factor IX operably linked to the GPIIb promoter could be used for tissue specific expression in vitro. However, as evidenced in Wang et al. (Blood Vol. 90, No. 3, pp. 1075-1082, 1997),at the time of the invention, successful implementation of gene therapy protocols for the *in vivo* production of factor IX were not routinely obtainable by those of skill in the art. Wang et al. states that human factor IX expression levels were either too low to be therapeutic or transient (see p. 1075, Col. 1, paragraph 2). Verma and Somia (Nature Vol. 389, pp. 239-242) also discuss the attempts at ex vivo gene therapy using factor IX and state that the appropriate enhancer-promoter combination is essential to obtaining sufficient levels of expression and that the search for such combinations is a case of trial and error for a given type of cell (see p. 240, paragraph bridging Cols. 2-3). In addition, those of skill in the art, as evidenced by Somia and Verma (Nature Reviews/Genetics 1:91-99, 11/2000), recognize that delivery vehicles still represent the Achilles heel of gene therapy, and that no single vector exists that has all of the attributes of an ideal gene therapy vector (see p. 91, Col. 1, lines 5-13, 1st paragraph).

Predictability/Unpredictability of the art

The success of gene therapy is highly unpredictable. Anderson (Nature 392: 25-30 (Suppl.) , 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-thearpy protocol has been successful in treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p. 30).

Quantity of Experimentation

In light of the highly complex and unpredictable nature of gene therapy, the state of the art which lacks any examples of expressing factor IX in vivo, the relative skill of those in the art who recognize the complexity and unpredictability of gene therapy protocols, the lack of examples or guidance in the Specification as to a protocol for the in vivo expression of factor IX, the quantity of experimentation required to express factor IX in vivo is considered undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the development of a vector that could successfully deliver and express a therapeutically effective amount of factor IX specifically in megakaryocytes in vivo. It is this additional research to develop a successful gene therapy protocol for factor IX that is required to practice the entire scope instant claim that constitutes undue experimentation.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
May 12, 2003

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